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Patterns of breast cancer mortality trends in Europe

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ABSTRACT

Objectives: To identify patterns of variation in breast cancer mortality in Europe (1980–2010), using a model-based approach.
Methods: Mortality data were obtained from the World Health Organization database and mixed models were used to describe the time trends in the age-standardized mortality rates (ASMR). Model-based clustering was used to identify clusters of countries with homogeneous variation in ASMR.
Results: Three patterns were identified. Patterns 1 and 2 are characterized by stable or slightly increasing trends in ASMR in the first half of the period analysed, and a clear decline is observed thereafter; in pattern 1 the median of the ASMR is higher, and the highest rates were achieved sooner. Pattern 3 is characterised by a rapid increase in mortality until 1999, declining slowly thereafter.
Conclusion: This study provides a general model for the description and interpretation of the variation in breast cancer mortality in Europe, based in three main patterns.

Introduction

Breast cancer is the leading cause of oncological death among women, in both economically developed and developing settings.[1] In Europe, in the last decades the mortality decreased in most countries,[2] along with rising incidence rates.[3]

An increasing incidence may be explained by trends towards a more frequent exposure to factors that contribute to a higher risk of breast cancer (e.g.: delayed childbearing, lower parity, use of postmenopausal hormone therapy, obesity, physical inactivity),[4,5] while the widespread use of mammographic screening further contributes to higher incidence rates.[5,6]

The decline in mortality rates has been attributed both to an increasing frequency of early diagnosis through mammography screening and access to more efficient treatments, including adjuvant chemotherapy or tamoxifen, besides improved radiotherapy and surgery.[7–11] The identification of clusters of countries with similar trends in breast cancer mortality may contribute to understand the impact, at a population level, of early detection and improved disease management. Previous attempts to describe breast cancer mortality patterns relied on criteria related to geographical,[12] social, economic or cultural[13–15] characteristics. Model-based clustering may allow a more meaningful grouping of the different settings with no *a priori* constraints, according to the magnitude of the mortality rates at onset of the observation period, as well as its trends.

Therefore, we aimed to identify patterns of variation in breast cancer mortality, using a model-based approach.

Methods

Breast cancer mortality data were obtained for 40 countries from the World Health Organization (WHO) database updated in November 24, 2011.[16] Albania, Bosnia and Herzegovina, Cyprus, Montenegro, The Former Yugoslav Republic of Macedonia, Serbia and Slovakia had data available for less than 20 calendar years between 1980 and 2010, and were excluded from our analyses (Fig. 1). In this period, different revisions of the International Classification of Diseases (ICD) were used; we extracted the number of deaths, corresponding to the codes A054 (ICD-8), B113 (ICD-9), C50 (ICD-10).

Mid-year estimates of the resident population were obtained from the 2010 revision of United Nations World Population

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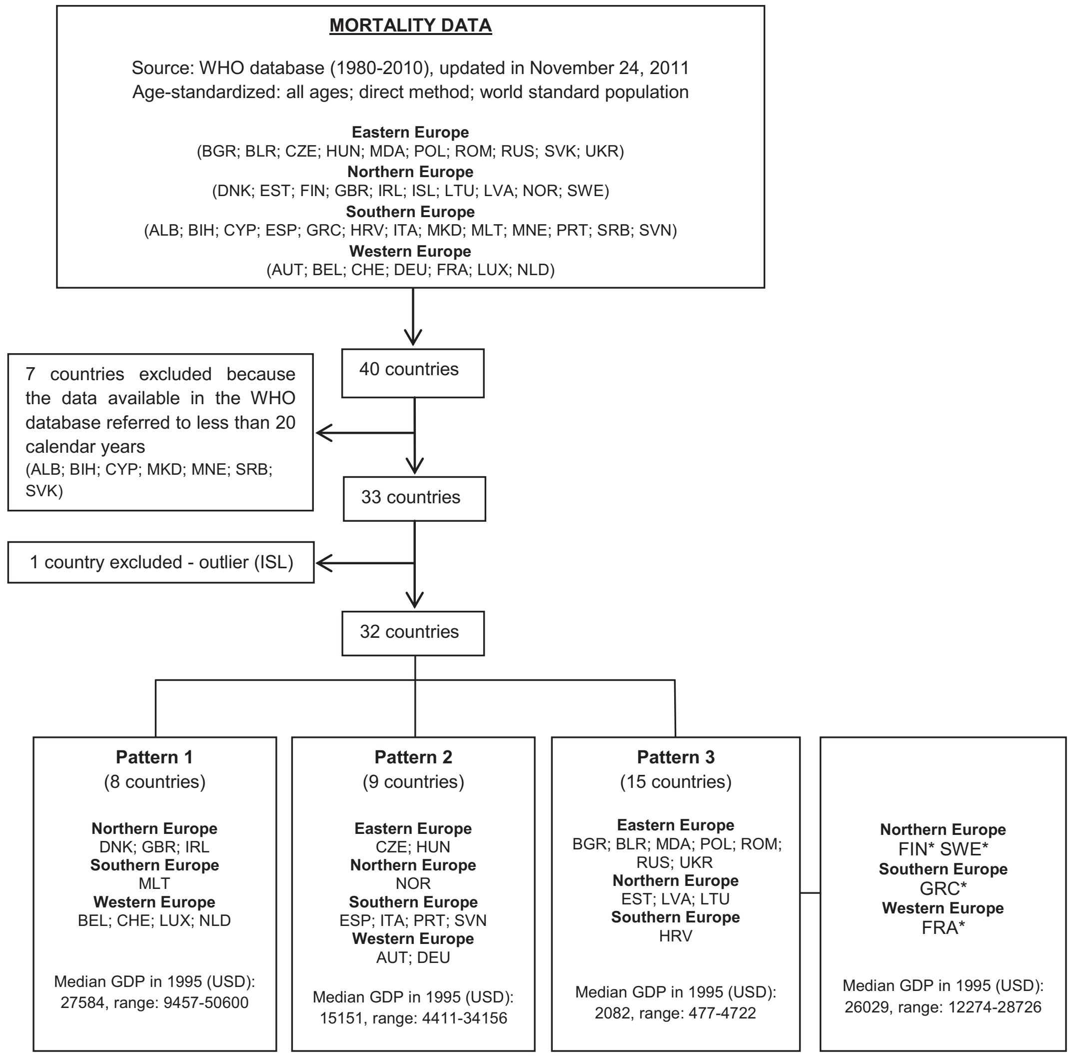


*Finland, France, Greece and Sweden had substantially higher GDP than the other countries included in pattern 3, and were treated separately to increase the homogeneity of this cluster

ALB=Albania; AUT=Austria; BEL=Belgium; BIH=Bosnia and Herzegovina; BGR=Bulgaria; BLR=Belarus; CHE=Switzerland; CYP=Cyprus; CZE=Czech Republic; DEU=Germany; DNK=Denmark; ESP=Spain; EST=Estonia; FIN=Finland; FRA=France; GBR=United Kingdom; GRC=Greece; HRV=Croatia; HUN=Hungary; IRL=Ireland; ISL=Island; ITA=Italy; LTU=Lithuania; LUX=Luxembourg; LVA=Latvia; MDA=Republic of Moldova; MKD=The Former Yugoslav Republic of Macedonia; MLT=Malta; MNE=Montenegro; NLD=The Netherlands; NOR=Norway; POL=Poland; PRT=Portugal; ROM=Romania; RUS=Russian Federation; SRB=Serbia; SVN=Slovenia; SVK=Slovakia; SWE=Sweden; UKR=Ukraine.

Fig. 1. Flowchart of the model-based approach used to identify breast cancer mortality patterns.

Prospects.[17] We computed age-standardized mortality rates (ASMR) for all ages, by the direct method, using the world standard population[18] as reference.

Mixed models[19] were used to describe the time trends in the ASMR, including random terms by country, for the intercept and for slope, quadratic and cubic terms. Iceland presented values three times the interquartile range above or below the median for at least one of the above coefficients and was excluded from further analyses (Fig. 1). These models were used to estimate the ASMR for the years with missing data, between 1980 and 2010 (Appendix 1).

Model-based clustering[20] was used to identify groups of countries that share similar time trends in the ASMR, while distinguishing them from other homogeneous groups of countries regarding the variation in mortality rates. According to this method, the data (intercept, slope, quadratic and cubic terms) are assumed to have a multivariate normal distribution, parameterized by their means and covariances, generated by clusters. The geometric features (orientation, volume and shape) of the distributions are estimated from the data, and can be allowed to vary between clusters, or constrained to be the same for all clusters.[21]

The most appropriate models were considered those allowing for the most homogeneous grouping of countries regarding their patterns of variation, as assessed by visual inspection of the country-specific trends, selected among those with the lowest Bayesian Information Criterion (BIC)[22] (Appendix 2).

To describe the patterns of variation that characterize each cluster, we computed the means of the predicted country-specific ASMR for each of the clusters identified, for every year within the period 1980–2010, and represented them graphically; for each cluster we also presented the median and percentile 25 and 75 of the rates in the beginning, middle and end of the period under analysis, as well as the percent variation in ASMR in the first and second half of the same period.

Data analysis was conducted using data from 33 European countries (Fig. 1), with the software R 2.14.1, using the packages *nlme*[23] and *mclust*[24] for mixed models analysis and model-based clustering, respectively.

The patterns identified through the model-based approach were further characterized according to gross domestic product (GDP) *per capita* in 1995 (the midpoint of the period under analysis); data were obtained from the World Bank database.[25]

Data on organized breast cancer screening activities in each country were obtained from published peer reviewed articles or official reports and used in the interpretation of the patterns, along with the trends in breast cancer incidence (Appendix 3). Age-standardized (world standard population) incidence rates (ASIR), and the corresponding standard errors, were abstracted from the Cancer Incidence in Five Continents database CI5plus, after the November 5, 2012 update,[26] for all the years with available data in the period 1970–2002; data were available for 18 of the European countries eligible for model-based clustering. We analysed trends in incidence rates for the age groups covered by the breast cancer screening programmes implemented in each country, if applicable, or the age group 50–69 years (defined according to European Council's guidelines for breast cancer screening[27]), as well as for the younger and older women than those eligible for screening. The annual percent change (APC), as well as significant changes in the linear trends of age-standardized incidence rates were assessed using the software Joinpoint Regression Program, version 3.5.3.[28] The number of joinpoints allowed was limited to a maximum of five (Table 2). For the United Kingdom (UK), incidence data were available only for Scotland and England.

Results

We identified three main patterns of breast cancer mortality trends in Europe, hereafter referred to as patterns 1, 2 and 3.

Patterns 1 and 2 are characterized by stable or slightly increasing trends in ASMR in the first half of the period under analysis, and a clear decline was observed thereafter; however, the median of the ASMR was higher for the countries included in pattern 1, throughout the whole period, and the highest rates were achieved sooner than in pattern 2. Pattern 1 comprises mostly countries from western and northern Europe, and all of them were high income countries [median GDP (USD): 27584, range: 9457–50600], while pattern 2 is more heterogeneous regarding the geographical distribution and GDP [median GDP (USD): 15151, range: 4411–34156] (Figs. 1 and 2 and Table 1).

Pattern 3 included 11 countries with GDP lower than 5000 USD, mainly eastern and northern European, and four countries (Finland, France, Greece and Sweden) with GDP higher than 12000 USD (Fig. 1). The former were characterized by the lowest median ASMR in 1980, which increased steeply during the first half of the period under analysis, and decreased thereafter, mostly after 1999 and at a slower pace than in patterns 1 and 2 (Fig. 2 and Table 1). Finland, France and Greece depicted slightly increasing trends in the first part of the period under study and a marked decline from that point onwards, resembling more closely patterns 1 and 2. However, in these countries the ASMR observed in 1980 were among the lowest in Europe (Appendix 1). Sweden presented a downward trend throughout the whole period, with a steeper decrease in the second half, which is a unique behaviour among all the countries analysed (Appendix 1). Therefore, these four countries were treated separately from all other included in pattern 3, to increase the homogeneity of this cluster.

Table 1
Characterization of the female breast cancer mortality patterns regarding the estimated age-standardized mortality rates (direct method, world standard population), all ages (ASMR), in 1980, 1995 and 2010, percent changes in rates in the periods 1980–1995 and 1995–2010, and highest rates and corresponding year observed between 1980 and 2010.

	Median (percentile 25; percentile 75)		
	Pattern 1	Pattern 2	Pattern 3[a]
ASMR[b]			
1980	25.5 (24.7; 26.5)	19.2 (16.8; 20.0)	12.7 (10.7; 14.2)
1995	25.5 (23.4; 26.4)	20.7 (18.2; 21.4)	16.0 (15.8; 17.6)
2010	17.4 (15.9; 18.0)	15.1 (14.1; 16.1)	15.8 (14.7; 16.1)
Variation in ASMR (%)[c]			
1980–1995	−3.3 (−7.7; 0.6)	8.0 (4.8; 14.6)	33.3 (24.9; 47.9)
1995–2010	−31.3 (−32.6; −30.4)	−23.9 (−24.9; −22.7)	−7.2 (−12.8; −2.2)
ASMR[d]			
Higher value observed	29.5 (27.3; 30.0)	22.1 (19.9; 22.5)	18.2 (16.5; 19.6)
Year of highest value	1986.5 (1985.5; 1991.5)	1993 (1991; 1994)	1999 (1994; 2002)

ASMR – Age standardized mortality rates (world standard population).
[a] The results referring to pattern 3 do not include data from Finland, France, Greece or Sweden.
[b] Model estimates.
[c] Computed from the model estimates.
[d] Observed data.

Over the last three decades there was a levelling of breast cancer mortality across Europe. In 1980 the median of the ASMR in the countries included in pattern 3 (excluding Finland, France, Greece and Sweden) was approximately half the observed for pattern 1, but only 10% lower in 2010 (Table 1).

Most of the countries included in patterns 1 and 2 have organized screening programmes, which were initiated before 1995 in more than half of those grouped in pattern 1 and in more than one third of those in pattern 2. Nearly two-thirds of the countries included in pattern 3 (excluding Finland, France, Greece and Sweden) had no organized screening implemented. Finland, France, Greece and Sweden had organized screening (Fig. 3).

In the age groups eligible for screening, among the countries with screening programmes implemented before 2002 (the last year with available date in CI5plus) there was a steep increase in the ASIR close to the year of screening onset, reflecting the increased detection of prevalent cancers, for England, Finland, the Netherlands, Norway, Scotland and Sweden; these countries started organized screening mostly in the 1980's and all have a participation rate of over 70%.[29,30] A similar increase was observed in Italy after 1995; despite having a screening programme implemented for the first time in 1985, only since 1996 the Italian Ministry of Health issued a nationally agreed protocol.[31] In the remaining countries the ASIR increased with time in all countries considered for this analysis, regardless of the existence of organized screening (Table 2).

Table 2
Characterization of countries regarding trends in age-standardized incidence rates by age groups, according to patterns of trends in breast cancer mortality rates.

	Country	Age groups[b]	ASIR[a]		Trends in ASIR[a]					
		(Years)	1988	2002	Period 1 APC (95%CI)	Period 2 APC (95%CI)	Period 3 APC (95%CI)	Period 4 APC (95%CI)	Period 5 APC (95%CI)	Period 6 APC (95%CI)
Pattern 1	Denmark	0–49	32.0	28.4	1970–1988 1.7 (1.1 to 2.3)	1988–2002 −1.1 (−1.8 to −0.4)				
		50–59	210.7	264.6	1970–2002 1.9 (1.7 to 2.1)					
		60+	272.9	378.6	1970–1986 0.9 (0.4 to 1.5)	1986–2002 2.5 (2.0 to 3.0)				
	England (UK)	0–49	27.1	29.5	1985–1992 1.8 (1.0 to 2.6)	1992–2002 0.2 (−0.2 to 0.6)				
		50–64	196.2	288.5	1985–1988 2.3 (−1.3 to 6.0)	1988–1991 12.6 (5.5 to 20.1)	1991–1994 −3.4 (−9.1 to 2.6)	1994–2002 2.2 (1.5 to 2.8)		
		65+	256.1	302.7	1985–2002 1.0 (0.7 to 1.2)					
	The Netherlands	0–49	29.2	39.4	1973–2002 1.1 (0.8 to 1.4)					
		50–69	203.8	319.0	1973–1991 0.8 (−0.2 to 1.9)	1991–1995 7.5 (−6.1 to 23.0)	1995–2002 −0.4 (−3.4 to 2.7)			
		70+	296.7	347.2	1973–2002 1.6 (1.0 to 2.1)					
	Scotland (UK)	0–49	26.7	26.8	1975–2002 0.3 (0.1 to 0.5)					
		50–64	188.0	288.1	1975–1988 1.2 (0.5 to 1.9)	1988–1991 12.1 (−0.6 to 26.4)	1991–2002 0.8 (0.1 to 1.6)			
		65+	254.7	271.9	1975–2002 1.0 (0.9 to 1.2)					
	Switzerland	0–49	23.7	26.3	1983–2002 0.6 (0.0 to 1.3)					
		50–70	221.6	298.7	1983–2002 3.1 (2.4 to 3.8)					
		70+	304.5	258.2	1983–2002 −0.9 (−1.6 to −0.3)					
Pattern 2	Austria	0–49	22.0	24.6	1988–2002 0.9 (−0.3 to 2.0)					
		50–69	199.3	244.5	1988–2002 1.9 (1.2 to 2.7)					
		70+	317.6	356.2	1988–2002 −1.0 (−2.5 to 0.7)					
	Czech Republic	0–44	9.9	10.1	1983–2002 0.3 (−0.3 to 0.9)					
		45–69	126.5	182.5	1983–2002 2.4 (2.1 to 2.7)					
		70+	192.7	280.9	1983–1995 3.6 (2.8 to 4.4)	1995–2002 0.7 (−0.8 to 2.2)				
	Germany	0–49	25.2	28.1	1970–2002 1.0 (0.7 to 1.4)					
		50–69	202.7	272.1	1970–1987 0.6 (−0.2 to 1.4)	1987–2002 2.9 (2.1 to 3.8)				
		70+	248.9	317.4	1970–2002 1.8 (1.5 to 2.1)					
	Italy	0–49	29.1	36.5	1988–2002 2.1 (1.6 to 2.6)					
		50–69	198.3	293.4	1988–1995 2.5 (0.5 to 4.5)	1995–1999 7.5 (0.9 to 14.5)	1999–2002 −2.5 (−8.2 to 3.6)			
		70+	247.1	282.9	1988–1991 −0.7 (−2.8 to 1.6)	1991–1995 3.7 (1.8 to 5.8)	1995–1999 1.8 (0.0 to 3.5)	1999–2002 −2.8 (−4.4 to −1.1)		
	Norway	0–49	21.7	23.1	1970–1996 1.3 (0.9 to 1.6)	1996–2002 −2.2 (−4.7 to 0.4)				
		50–69	165.5	287.1	1970–1990 0.8 (0.2 to 1.4)	1990–2002 5.0 (3.9 to 6.0)				
		70+	262.0	233.7	1970–1985 2.2 (1.5 to 2.9)	1985–2002 −0.3 (−0.8 to 0.2)				
	Spain	0–49	20.8	26.3[c]	1985–2000 2.4 (1.8 to 3.1)					

(continued on next page)

Table 2 (*continued*)

	Country	Age groups[b] (Years)	ASIR[a] 1988	ASIR[a] 2002	Trends in ASIR[a] Period 1 APC (95%CI)	Period 2 APC (95%CI)	Period 3 APC (95%CI)	Period 4 APC (95%CI)	Period 5 APC (95%CI)	Period 6 APC (95%CI)
		50–64	120.3	211.0[c]	1985–2000					
		65+	157.9	193.4[c]	3.2 (2.4 to 3.9)	1985–2000				
	2.1 (1.4 to 2.7)									
	Slovenia	0–49	18.4	21.8	1970–2002 1.3 (0.9 to 1.6)					
		50–69	152.8	205.7	1970–2002 2.4 (2.2 to 2.7)					
		70+	197.7	259.0	1970–2002					
3.1 (2.8 to 3.4)										
Pattern 3	Estonia	0–49	16.4	21.0	1970–2002 1.7 (1.3 to 2.1)					
		50–59	103.0	154.5	1970–2002 2.2 (1.8 to 2.6)					
		60+	105.6	170.1	1970–2002 2.9 (2.6 to 3.2)					
	Finland	0–49	24.1	27.1	1970–1995 2.6 (2.4 to 2.9)	1995–2002 −0.6 (−2.0 to 0.8)				
		50–59	200.7	316.7	1970–1984 2.2 (1.5 to 2.9)	1984–1989 7.7 (3.7 to 11.9)	1989–1993 0.2 (−5.3 to 6.0)	1993–2002 4.4 (3.5 to 5.3)		
		60+	229.7	289.7	1970–2002 1.9 (1.6 to 2.1)					
	France	0–49	32.5	32.1	1983–1994 2.6 (1.7 to 3.6)	1994–2002 −2.8 (−4.0 to −1.5)				
		50–74	229.5	361.7	1983–2002 2.9 (2.5 to 3.4)					
		75+	240.7	277.7	1983–2002 1.2 (0.7 to 1.7)					
	Latvia	0–49	16.6	17.3	1988–2002 1.5 (0.2 to 2.8)					
		50–69	111.0	153.8	1988–2002 3.0 (2.4 to 3.6)					
		70+	83.2	153.3	1988–2002 5.4 (3.9 to 6.9)					
	Lithuania	0–49	16.3	16.8	1978–2002 1.3 (0.9 to 1.8)					
		50–69	95.8	136.1	1978–2002 2.9 (2.5 to 3.4)					
		70+	83.3	156.6	1978–2002 4.4 (3.8 to 5.0)					
	Poland	0–49	18.1	19.6	1988–1995 3.4 (1.1 to 5.8)	1995–2002 −1.6 (−3.6 to 0.5)				
		50–69	130.5	200.2	1988–2002 3.0 (2.3 to 3.7)					
		70+	169.2	209.0	1988–1995 4.9 (1.2 to 8.8)	1995–2002 −1.8 (−4.6 to 1.1)				
	Sweden	0–49	25.3	25.9	1970–2002 0.9 (0.8 to 1.1)					
		50–69	209.4	302.6	1970–1978 2.1 (1.3 to 2.8)	1978–1986 0.0 (−0.9 to 0.9)	1986–1990 8.8 (5.5 to 12.3)	1990–1993 −2.4 (−8.0 to 3.5)	1993–2002 3.0 (2.5 to 3.5)	
		70+	288.9	282.5	1970–1973 −2.4 (−6.9 to 2.5)	1973–1979 3.0 (1.0 to 5.0)	1979–1984 −2.4 (−4.9 to 0.1)	1984–1987 3.5 (−4.4 to 12.1)	1987–1995 −1.5 (−2.5 to −0.5)	1995–2002 1.3 (0.2 to 2.3)

[a] ASIR – age-standardized incidence rates (world standard population).
[b] Three groups were considered: age groups covered by the organized breast cancer screening implemented in each country; age groups below the ages eligible for screening; age groups above the ages eligible for screening. In countries with no organized programme(s), the recommendations of the European Council's guidelines were considered as reference (50–69 years).
[c] Age-standardized incidence rates in the last year with data available (2000).

Discussion

We identified three patterns that summarize the temporal trends in breast cancer mortality across European countries. Despite an overall downward trend observed in recent years throughout Europe, the patterns differ in the highest rates achieved and the year of inflection in the ASMR trends. A levelling of breast cancer mortality was observed across Europe over the last three decades.

The declines in mortality rates could be explained by earlier diagnosis and mostly access to better management of the cases.

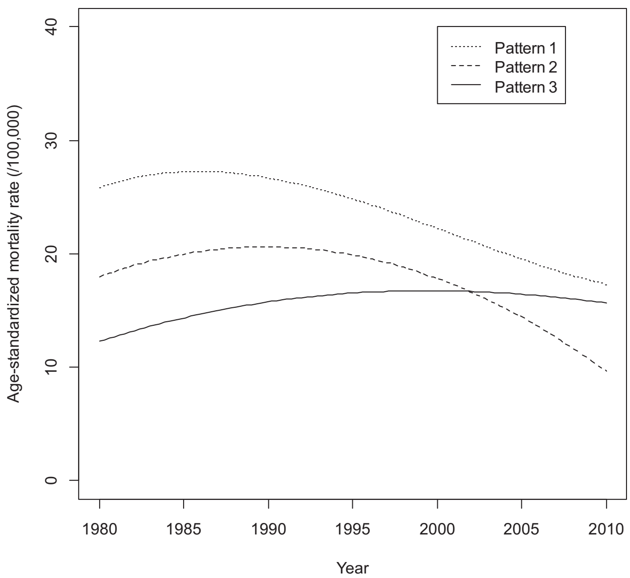
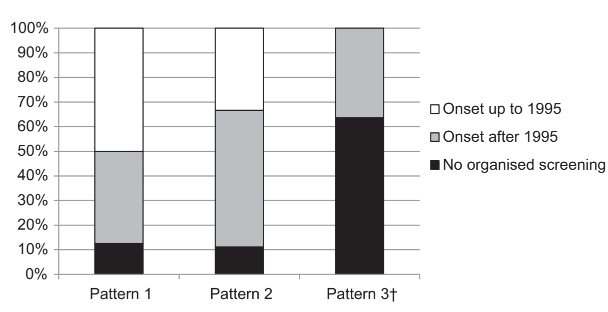


Fig. 2. Age-standardized (direct method, world standard population) breast cancer mortality rates *, all ages, for each pattern† identified.

Despite the observations that breast cancer incidence rates are no longer increasing or even declining in some settings and specific age-groups,[3,32] in all the European countries analysed, incidence is still increasing, or not varying significantly, in the age groups with the largest contribution to the overall rates. These trends are largely influenced by diagnosis and screening practices; estimates of excess incidence due to screening range from 11–19%[33] to 15–25%.[34,35] Furthermore, these trends depend on the frequency and changes of risk factors such as early menarche, delayed childbearing, lower parity, use of postmenopausal hormone therapy and obesity.[36,37] Most of these risk factors are still more common in more affluent settings and are increasing in the less affluent.[38] This is in accordance with the observation of the highest ASIR in the countries included in pattern 1, the one presenting the highest median GDP, and the lowest ASIR in the less affluent countries from pattern 3.

In pattern 3 (excluding Finland, France, Greece and Sweden), although the inflection in the mortality rates occurred later than in the remaining countries, the ASMR peaked at lower values. Also, in pattern 2 the decline started later and at lower ASMR than that observed for pattern 1. These distinctive features suggest that the implementation of effective cancer control measures occurred in different times in settings with different risk profiles for breast cancer.



* We considered the existence of organized screening, regardless of its coverage or participation rates.

† The results referring to pattern 3 do not include data from Finland, France, Greece or Sweden.

Fig. 3. Proportion of countries with no organized breast cancer screening, or screening programmes set up in different time periods*, for each pattern identified.

The best estimates of the impact of screening mammography on breast cancer mortality range from 10% on regional mortality data,[39] to 20% on trial results.[33] Since the fall in mortality in pattern 1 exceeded 30%, this indicates that most of the decline is due to improved management and treatment. Also, in most of the countries considered in our analyses the lag between onset of screening and the inflection of the mortality trends was shorter than the 7–12 years that could be expected[40] if the screening programmes had an important contribution to the initial declines. However, no inference is possible regarding their longer term effects on mortality. Furthermore, these results do not exclude the potential contribution of opportunistic screening for the mortality reduction. In most of the countries from patterns 1 and 2 and in the more affluent from pattern 3, the incidence rates increased more steeply in the age-groups eligible for screening, suggesting that mammography screening was widespread, to higher or lesser extent, even in the absence of screening programmes. In fact, countries with no programmes implemented or with lower participation rates are known to have a considerable volume of "opportunistic" mammography testing, namely Belgium, Czech Republic, France, Germany, Hungary, Italy, Malta and Switzerland.[29,41–43] Although the balance between benefits and risks of screening is less favourable in opportunistic mammography testing than in organized programmes,[44,45] the former may also have a favourable impact on mortality.[46]

There has been a substantial improvement in breast cancer treatments since the 1960's, when radical mastectomy only was the predominant treatment option.[47] By the late 1980's, in many developed countries tamoxifen and polychemotherapy were used as adjuvant therapy after surgical treatment for primary breast cancer; therefore, an effect in mortality trends should occur by early 1990's,[48] which makes the declining mortality trends experienced in several countries compatible with the increase in use of systemic adjuvant therapies. The current therapies, more effective and more age- and tumour-specific,[8,11] as well as the integrated organization of the provision of breast cancer care[36] contributed to a sustained decline in mortality rates in the last two decades, especially in countries in patterns 1 and 2.

Between 1980 and 2010, three different revisions of the International Classification of Disease (ICD) were used to code the underlying cause of death. Although changes in coding could induce some variation of rates, it is not likely to compromise the comparability of data over time, since differences between revisions are minor regarding breast cancer.[49,50]

Our study relied on an original approach to summarize the trends in cancer mortality rates in different countries. Model-based clustering has several advantages over standard cluster approaches. It provides cluster solutions with ten different covariance structures, while the most popular heuristic clustering methods (Ward's and K-means) only allow one type covariance structure,[20] and also allows the choice of the model and the number of clusters to be recast as statistical model choice problems based on information criteria.

Based on the BIC the 7-cluster solution was the best, followed by the 2- and 3-cluster solutions, with similar BIC values. When seven clusters were considered, six of these clusters included only 3 or 4 countries, and were considered too specific to constitute a general pattern. Between the 2- and 3-cluster solutions we opted for the latter, because it yielded groups of countries clearly more homogeneous regarding the patterns of variation in breast cancer mortality.

The reliability of the model-based clustering was evaluated by tenfold cross validation.[51] The sample was divided in ten partitions, and each of the subsets of nine out of the ten partitions was used to fit ten different models (data not shown). The agreement between the predictions from these models and those from the model based on the complete dataset was moderate[52] (kappa = 0.55). This, reflects the fact that some countries depict a pattern of variation that does not fit so well in the main patterns, as described for Finland, France, Greece and Sweden (after excluding these four countries the kappa increased to 0.61), although some misclassification may be anticipated for other countries (e.g. Poland). Furthermore, the 4-cluster solution did not accommodate the countries that were a bad fit for pattern 3 in the additional pattern, which supports our option for only 3 main clusters that reflect quite closely the trends in the majority of the European countries analysed.

Despite the limitations described above, the fact that this model provides an unconstrained analysis of mortality patterns is one of the major strengths of this paper. Our study adds to previous research on this topic the identification of three clusters of countries that are homogeneous regarding the variation in breast cancer mortality, while remaining heterogeneous regarding the distribution of variables traditionally used for an *a priori* grouping of the countries, namely geographical region, economic development or standards of care. Although Northern European, Southern European and Eastern European countries are predominant in patterns 1, 2 and 3, respectively, all clusters include countries from different European regions. The median GDP and the proportion of countries with organized screening decreases from pattern 1 to 3, but there is a clear overlap of the distribution of these variables across patterns, especially between patterns 1 and 2.

We used incidence data obtained from the CI5plus database to ensure some homogeneity of data quality. However, these data are based on a coverage of less than 15% of the country population from Austria, France, Germany, Italy, Netherlands, Poland, Spain and Switzerland.[53] Since incidence data was used mainly to interpret the patterns, this has not compromised the validity of our findings.

In conclusion, this study provides a general model for the description and interpretation of the variation in breast cancer mortality in Europe, based in three main patterns.

Conflict of interest statement

None declared.

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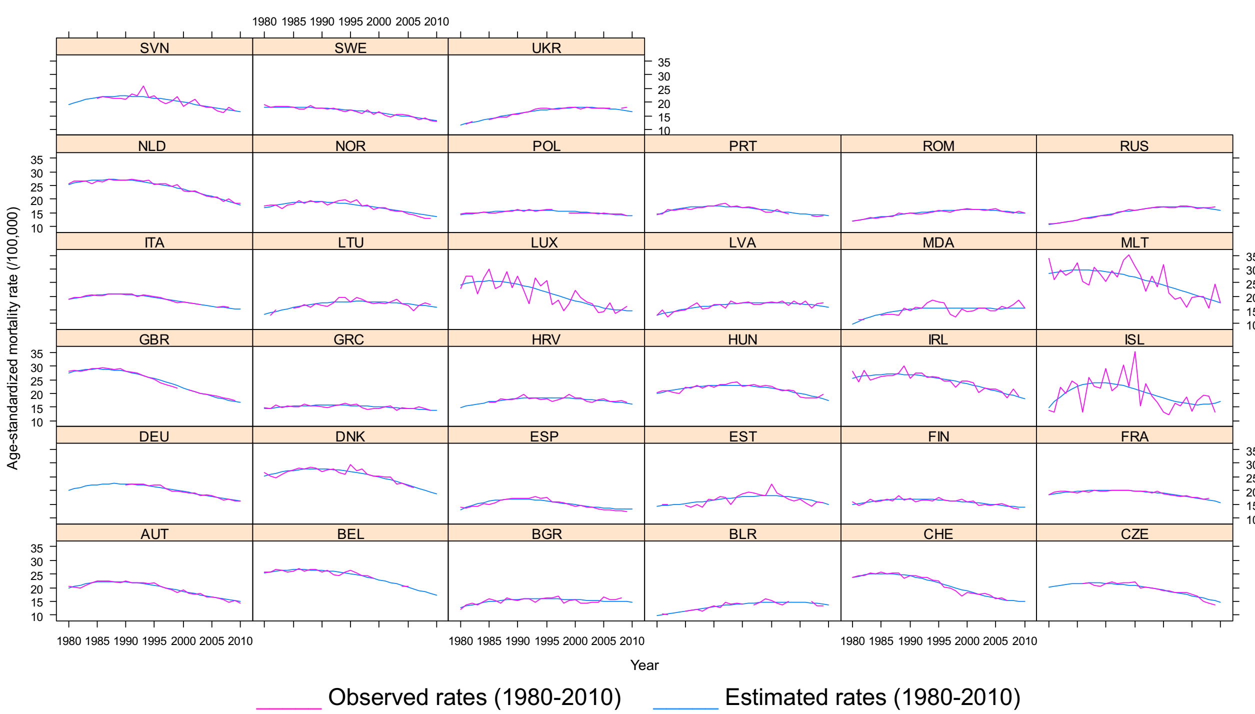
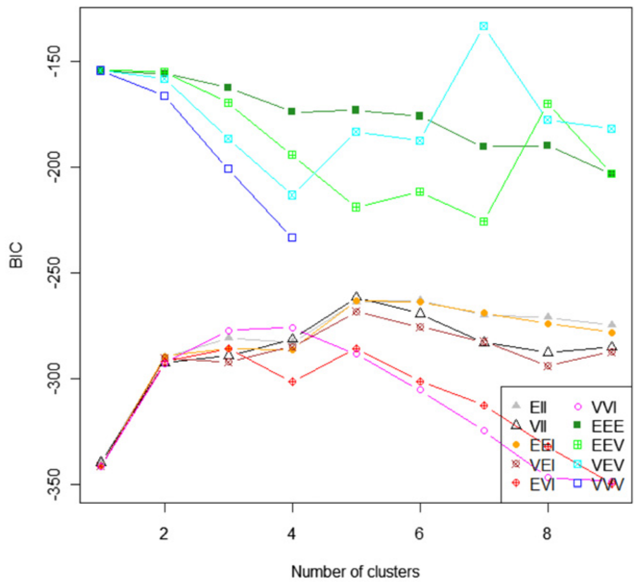
Appendix 1. Observed and predicted breast cancer age standardized mortality rates (direct method, World standard population), all ages.



AUT=Austria; BEL=Belgium; BGR=Bulgaria; BLR=Belarus; CHE=Switzerland; CZE=Czech Republic; DEU=Germany; DNK=Denmark; ESP=Spain; EST=Estonia; FIN=Finland; FRA=France; GBR=United Kingdom; GRC=Greece; HRV=Croatia; HUN=Hungary; IRL=Ireland; ISL=Island; ITA=Italy; LTU=Lithuania; LUX=Luxembourg; LVA=Latvia; MDA=Republic of Moldova; MLT=Malta; NLD=The Netherlands; NOR=Norway; POL=Poland; PRT=Portugal; ROM=Romania; RUS=Russian Federation; SVN=Slovenia; SWE=Sweden; UKR=Ukraine.

Appendix 2. Identification of the patterns by model-based clustering.



BIC – Bayesian Information Criteria (the plot depicts the BIC value multiplied by minus one)
EII – Equal volume, equal shape, non applicable orientation;
VII – Variable volume, equal shape, non applicable orientation;
EEI – Equal volume, equal shape, coordinate axes orientation;
VEI – Variable volume, equal shape, coordinate axes orientation;
EVI – Equal volume, variable shape, coordinate axes orientation;
VVI – Variable volume, variable shape, coordinate axes orientation;
EEE – Equal volume, equal shape, equal orientation;
EEV – Equal volume, equal shape, variable orientation;
VEV – Variable volume, equal shape, variable orientation;
VVV – Variable volume, variable shape, variable orientation.

Appendix 3. Characterization of countries regarding organized screening activities, by patterns of trends in breast cancer mortality rates.

	Country	Organized screening			
		Year first programme started	National coverage (year)	Age group (years)	References
Pattern 1	Belgium	2001	Yes	50–69	29
	Denmark	1991	No	50–59	29,54,55
	Ireland	2000	Yes	50–64	56–58
	Luxembourg	1992	Yes	50–69	29
	Malta	–	No	–	41,59
	Netherlands	1989	Yes (1997)	50–69/75[a]	29,60
	Scotland (UK)	1988	Yes (1991)	50–64/70[b]	30
	England (UK)	1988	Yes (1995)	50–64/70[c]	61
	Switzerland	1999[d]	No	50–70	29,44,59,62
Pattern 2	Austria	2008[e]	No	50–69	63,64
	Czech Republic	2002	Yes	45–69[f]	41,43,59
	Germany	2005	2009	50–69	29,41,65
	Hungary	2002[g]	Yes	45–65	41,66
	Italy	1985	No	45/50–69[h]	29,31,65,67
	Norway	1996	2004	50–69	29,68
	Portugal	1990	No	45–69	29
	Spain	1990	2000	45/50–64/69[i]	69
Pattern 3	Slovenia	–	No	–	33
	Belarus	–	No	–	70
	Bulgaria	–	No	–	23,29,32
	Croatia	2006	Yes	50–69	71,72
	Estonia	2003	Yes	50–59	59
	Finland	1987	Yes	50–59	29,73
	France	1989	2004	50–74	29,74
	Greece	2004	No	40-69	29,75
	Latvia	–	No	–	59
	Lithuania	2006	Yes	50–69	56,59
	Poland	2007	Yes	50–69	56,59
	Rep. of Moldova	–	No	–	–
	Romania	–	No	–	59
	Russian Fed.	–	No	–	–
	Sweden	1986	1997	40/50–69/74[j]	29,56,76
	Ukraine	–	No	–	–

(continued on next page)

(continued)

[a] Women eligible in the Netherlands: 50–69 years; 70–75 included since 1998.
[b] Women eligible in Scotland: 50–64 years; extended to 70 in 2003/04.
[c] Women eligible in the United Kingdom: 50–64 years; by 2005 women aged 50–70 years were being screened.
[d] A pilot programme started in Switzerland in 1993 in canton Vaud.
[e] Tyrol (Austria): spontaneous mammography screening has an overall participation of 75% and was set up around 1993; in 2008 an organized programme started comprising the whole state.
[f] Women eligible in Czech Republic: since 2010 there is no upper age limit.
[g] Hungary: a pilot breast screening programme was established in 1995.
[h] Women eligible in Italy: 50–69 years; several programmes include women over 70 and some invite women 45–49 years.
[i] Women eligible in Spain: 50–65 years; some regions include women up to 69 and some invite women over 45 years.
[j] Women eligible in Sweden: 100% of counties invite 50–69 years; 60–70% start at age 40 and approximately 50% of counties invite age group 70–74.

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